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RESEARCH ARTICLE

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Management and outcomes of patients with recurrent neuroendocrine liver metastasis after curative surgery: An international multi-institutional analysis

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Objective: We sought to characterize the treatment, as well as define the long-term outcomes, of patients with recurrent neuroendocrine liver metastasis (NELM).

Methods: Between 1990 and 2014, 322 patients undergoing curative intent liver surgery for NELM were identified from a multi-institutional database. Recurrences were classified as intrahepatic, extrahepatic, and both intra- and extra-hepatic.

Results: Overall, median, 1-, 5-, 10-year DFS were 3.1 years, 75.5%, 40.4%, and 32.1%, respectively. After curative intent liver surgery, 209 patients (64.9%) recurred within a median follow-up of 4.5 years, while 113 (35.1%) patients were alive without disease with a follow-up time ≥3 years. The site of recurrence was intrahepatic only (n = 111, 65.7%), extrahepatic only (n = 19, 11.2%), or intra- and extra-hepatic (n = 39, 23.1%). Compared with intrahepatic only recurrence, extrahepatic only, and combined intra- and extra-hepatic recurrence were associated with a worse long-term outcome (10-year OS: intrahepatic only, 42.5%, 95%CI, 24.9-59.0 vs extrahepatic only, 0% and combined intra- and extra-hepatic, 21.5%, 95%CI, 5.3-44.0) (P < 0.001). Most patients were treated with repeat surgery (n = 49, 36.6%), while 34 (23.5%) patients received a somatostatin analogue, 27 (18.6%) systemic cytotoxic chemotherapy, and 27 (21.4%) patients had intra-arterial therapy. Ten-year OS among patients who underwent repeat surgery or intra-arterial treatments was 60.3% (95%CI, 34.1-78.8) and 52.0% (95%CI, 30.6-69.9), respectively. Patients who received somatostatin analogues (45.9% 95%CI, 22.3-66.9) or systemic chemotherapy (0%) had a shorter long-term survival (P = 0.001).

Conclusion: Recurrence after surgery for NELM occurred among half of patients. Repeat liver resection for recurrence may offer a reasonable 5-year survival benefit.

KEYWORDS
NELM, recurrence, surgery

1 | INTRODUCTION

Neuroendocrine tumors arise from cells originating from the neuroectoderm that contain secretory granules producing ectopic hormones. The most common gastro-entero-pancreatic neuroendocrine tumors (GEP-NET) are carcinoid, insulinomas, gastrinomas, somatostatinomas, glucagonomas, and vipomas. GEP-NET can be either sporadic or part of the multiple neuroendocrine neoplasia type 1 (MEN type 1) syndrome. Previously regarded as rare, the incidence of GEP-NET ranges from 2.5 to 4.5 per 100 000 and the incidence is increasing

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worldwide.[1] The vast majority of patients with GEP-NET are diagnosed with either locally advanced or metastatic disease. In fact, while the natural history of many GEP-NET can be indolent, up to 60-90% of patients develop liver metastasis during the course of their disease.[2] The presence of neuroendocrine liver metastases (NELM) can adversely impact patient quality of life via hormone secretion, as well as be associated with worse long-term outcomes.[3] Specifically, the 5-year overall survival (OS) of patients with NELM ranges from 13% to 54% versus 75% to 99% for patients with non-metastatic NET.[4–6] As such, treatment of NELM plays a central role in the management of patients with NET.[7]

While management strategies for NELM include non-surgical approaches such as intra-arterial (IAT) or systemic targeted agents,[8–14] as well as octreotide and tyrosine kinases inhibitors,[11–13] surgery offers the best potential for cure.[6,15,16] Surgical resection of NELM has been associated with 5-year OS ranging from 61% to 76% and 10-year survival of 35% to 51%.[17,18] Our group had previously reported that statistical cure following resection of NELM was 44% within 5.1 years after surgery.[19] These data suggest, however, that many patients experience recurrence. In particular, intrahepatic disease progression or recurrence has been reported to be as high as 70-90% within 5 years, depending on initial NELM tumor burden.[14,18]

The preferred management of patients with recurrent NELM following an initial surgical resection remains controversial. Several studies have reported on the safety and efficacy of repeat surgery in the treatment of colorectal liver metastasis, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma.[20–23] Data on repeat surgical management of recurrent NELM are lacking, however. As such, the objective of the current study was to define the incidence and pattern of recurrent NELM following initial surgical resection. In addition, we sought to characterize the treatment of recurrent NELM and define treatment-specific long-term outcomes.

2 | MATERIALS AND METHODS

2.1 | Patient demographic and clinical data

Between 1990 and 2014, 322 patients undergoing curative intent liver surgery for NELM were identified from a multi-institutional database (Johns Hopkins Hospital, Baltimore, MD; Scientific Institute San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; Stanford University, Stanford, CA; University of Virginia, Charlottesville, VA; Washington University, School of Medicine, St Louis, MO; Curry Cabral Hospital, Lisbon, Portugal; Emory University, Atlanta, GA). Only patients with histologically confirmed NELM or patients with radiological and clinical features highly suspicious for NELM were included in the study cohort. Patients who underwent curative intent surgery as initial treatment of NELM were identified and included; patients who received palliative surgical therapy or a non-surgical treatment (eg, IAT and/or only somatostatin analogs/tyrosine kinase inhibitors) were excluded. Patients who died within 30 days after surgery and patients with missing follow-up information were excluded. The Institutional Review Board of each participating institution approved the study.

Standard patient demographic and clinicopathologic data were collected including age, gender, race, symptoms, site, and management of primary tumor, time to development of liver metastasis, number of NELM and presence of extrahepatic metastasis were collected. Data regarding treatment details of the primary tumor were also collected including type of surgery and receipt of adjuvant chemotherapy and radiotherapy. Data on the initial surgical treatment of NELM, including intent of treatment, type of liver resection, extent of hepatic resection and timing between primary resection and diagnosis/treatment of NELM were recorded.

Date of last follow-up, vital status and recurrence-related information were collected on all patients. Recurrence was defined as the presence of a biopsy-proven recurrence or mass on imaging that had features highly suspicious of tumor recurrence. Data on site and number of NELM, as well as the disease-free interval (defined as the time from the date of initial operation to the development of recurrent disease) was recorded. Recurrences were classified as intrahepatic, extrahepatic, and both intra- and extra-hepatic. Data on treatment of recurrent NELM were also collected and categorized as repeat surgery, somatostatin analogue therapy, systemic cytotoxic chemotherapy, or IAT. IAT consisted of transarterial chemoembolization (TACE), bland transarterial embolization (TAE), drug eluting beads (DEB), or yttrium-90 (Y-90).

2.2 | Statistical analysis

Continuous and categorical variables were reported as medians with interquartile ranges (IQR) and as whole numbers and percentages, respectively. The distributions of categorical variables were compared using the Fisher's exact test while continuous variables were compared using the Mann-Whitney *U*-test. OS was defined as the time interval between the date of treatment and the date of death. Time was censored at the date of last follow-up assessment for all patients who were alive. Disease-free survival (DFS) was defined as the time interval between the date of surgery and the date of recurrence. Time was censored at the date of the last follow-up for patients who were noted to be free from disease. A P-value <0.05 was considered to be statistically significant. For statistical analysis, STATA software (StataCorporation, 2011, MP—Parallel Edition), and R CRAN software (v. 3.2.2, 2015) with the packages "survival," "Hmisc," "rms," and "ROCR" were used.

3 | RESULTS

3.1 | Clinicopathological and treatment characteristics

Among the 322 patients who met inclusion criteria, 209 (64.9%) patients developed a recurrence with a median follow-up of 4.5 years. Baseline characteristics of patients who recurred after curative-intent therapy for NELM are summarized in Supplementary Table S1. Median patient age was 58 years (IQR 49.0-67.0) and the majority of patients were male (n = 164, 50.9%). Most primary NET were pancreatic

TABLE 1 Timing of recurrence (n = 322)

Variable	*N* (%)	*N* (%)	*N* (%)	*P*-value
Timing of recurrence	No recurrence	Early recurrence	Late recurrence	
	N = 113	*N* = 152	*N* = 57	
Age, years, median (IQR)	59.3 (48.3-68.2)	58.0 (49.0-66.8)	57.9 (53.0-65.0)	0.84
Gender				0.56
Male	53 (32.3%)	81 (49.4%)	30 (18.3%)	
Female	60 (37.9%)	71 (44.9%)	27 (17.2%)	
Location of primary NET				0.005
Gastrointestinal	48 (31.6%)	81 (52.6%)	24 (15.8%)	
Pancreas	49 (33.8%)	66 (45.5%)	30 (20.7%)	
Other	16 (69.6%)	5 (21.7%)	2 (8.7%)	
Functional status				
Non-functional	26 (16.3%)	98 (61.3%)	36 (22.5%)	<0.001
Functional	47 (48.9%)	37 (38.5%)	12 (12.5%)	
Grade of differentiation				0.006
Well	65 (48.5%)	47 (35.1%)	22 (16.4%)	
Moderate	22 (34.4%)	35 (54.7%)	7 (10.9%)	
Poor	11 (22.5%)	28 (57.1%)	10 (20.4%)	
Lymph node status				<0.001
N0	83 (60.2%)	38 (27.5%)	17 (12.3%)	
N1	25 (16.5%)	96 (63.6%)	30 (19.9%)	
Synchronous disease				0.015
No	60 (44.1%)	54 (39.7%)	22 (16.2%)	
Yes	53 (28.7%)	97 (52.4%)	35 (18.9%)	
Treatment before liver surgery				<0.001
None	70 (32.4%)	104 (47.7%)	43 (19.9%)	
Octreotide	32 (64.0%)	15 (30.0%)	3 (6.0%)	
Chemotherapy	4 (19.4%)	16 (58.1%)	5 (22.6%)	
Liver involvement				<0.001
≥50%	62 (27.6%)	118 (52.4%)	45 (20.0%)	
<50%	48 (71.6%)	16 (23.9%)	3 (4.5%)	
Location				0.31
Unilobar	25 (21.9%)	64 (56.1%)	25 (21.9%)	
Bilobar	50 (31.1%)	85 (51.2%)	31 (18.7%)	
Intraoperative tumor ablation				0.005
No	100 (39.7%)	108 (42.9%)	44 (17.5%)	
Yes	13 (19.1%)	42 (61.8%)	13 (19.1%)	
Extrahepatic disease at diagnosis				0.001
No	111 (38.3%)	132 (45.5%)	47 (16.2%)	
Yes	2 (6.3%)	20 (65.5%)	10 (31.3%)	
Margin status				<0.001
R0	102 (44.8%)	96 (42.4%)	34 (12.9%)	
R1	15 (18.9%)	46 (58.2%)	18 (22.9%)	
Adjuvant therapy				<0.001
None	54 (39.1%)	62 (44.9%)	22 (15.9%)	
Octreotide	13 (17.6%)	42 (56.8%)	19 (25.7%)	
Chemotherapy	3 (8.3%)	28 (77.8%)	5 (13.9%)	

(Continues)

TABLE 1 (Continued)

Variable	N (%)	N (%)	N (%)	P-value
Site of recurrence				0.036
Intrahepatic only	—	88 (79.3%)	23 (20.7%)	
Intra- and extrahepatic	—	31 (79.5%)	8 (20.5%)	
Extrahepatic only	—	10 (52.6%)	9 (47.4%)	
Overall survival, 10-year (95%CI)	—	41.8% (29.2-53.8)	65.2% (47.3-78.3)	<0.001

(*n* = 145, 45.3%) or gastrointestinal (*n* = 153, 47.5%) in origin. At the time of diagnosis, 185 (57.6%) patients had synchronous metastatic disease. The majority of patients had bilateral hepatic metastases (*n* = 166; 59.3%), which often involved more than 50% of the liver parenchyma (*n* = 225; 77.1%). Overall, 32 (9.9%) patients had extrahepatic metastases. The majority of patients (*n* = 217; 74.3%) did not receive preoperative treatment prior to the initial surgery; a subset of patients did receive a somatostatin analog (*n* = 50; 17.1%) or cytotoxic chemotherapy (*n* = 25; 8.6%).

On final pathology, 151 (52.2%) patients had at least one metastatic lymph node (N1). Margin status was R0 in the majority of patients (*n* = 232; 74.6%), while roughly a quarter of patients (*n* = 79; 25.4%) had an R1 margin. The tumor was either well-differentiated (*n* = 134; 54.3%), moderately differentiated (*n* = 64; 25.9%), or poorly differentiated (*n* = 49; 19.8%). Roughly half of patients received adjuvant therapy with either a somatostatin analog (*n* = 74, 29.8%) or systemic cytotoxic chemotherapy (*n* = 36, 14.5%).

3.2 | Factors associated with recurrence and timing of recurrence

Overall, median, 1-, 5-, 10-year DFS were 3.1 years, 75.5%, 40.4%, and 32.1%, respectively. After curative intent liver surgery, 209 patients (64.9%) recurred, while 113 (35.1%) patients were alive without disease with a follow-up time ≥3 years.

Patients with a pancreatic or gastrointestinal primary NET had a higher incidence of recurrence (pancreatic NET: *n* = 96; 66.2% and gastrointestinal NET: *n* = 105; 68.4%) versus patients who had a primary NET from a non-pancreatic or gastrointestinal origin (other NET: *n* = 7, 30.4%; Table 1). In addition, patients with a primary pancreatic NET had higher risk of a late recurrence (*n* = 30, 20.7%) compared with either patients who had gastrointestinal NET (*n* = 24, 15.8%) or a primary NET from another origin (*n* = 2, 8.7%) (*P* < 0.05). Tumor grade was also associated with the incidence of recurrence (well-differentiated: *n* = 69, 51.5% vs moderately differentiated: *n* = 42, 65.6% vs poorly differentiated: *n* = 38, 77.5%) (*P* = 0.006). Other factors associated with recurrence included lymph node status (N0: *n* = 55, 39.8% vs N1: *n* = 126, 83.5%), ≥50% of liver involvement (<50%: *n* = 19, 28.4% vs ≥50%: *n* = 163, 72.4%), and margin status (R0: *n* = 130, 55.3% vs R1: *n* = 64, 81.1%) (all *P* < 0.05). Among the 209 patients who recurred, 152 (72.7%) had an early recurrence (≤3 years), whereas 57 (27.3%) experienced a late recurrence (>3 years). Several clinical and tumor characteristics were associated with the timing of recurrence (Table 1). For example, patients who had an R0 versus R1 margin had a comparable incidence of early recurrence (R0, *n* = 89, 42.4%; R1, *n* = 46, 58.2%), while R1 patients had almost a twofold increase incidence of late recurrence (R0, *n* = 27, 12.9%; R1, *n* = 18, 22.9%) (*P* < 0.001). The incidence of both early (<3 years) and late (≥3 years) recurrence was nearly double among patients with a non-functional NET (early: *n* = 98, 61.3%; late: *n* = 36, 22.5%) compared with patients who had a functional NET (early: *n* = 37, 38.5%; late: *n* = 12, 12.5%) (*P* < 0.001). In addition, when stratified by extent of liver disease, the incidence of recurrence was double in the early time period (<50%, *n* = 16, 23.9% vs ≥50%, *n* = 118, 52.4%) and increased to almost fourfold in the late time period (<50%, *n* = 3, 4.5% vs. ≥50%, *n* = 45, 20.0%) (*P* < 0.001).

3.3 | Site of recurrence

Data were available on the specific site of recurrence for 169 out of the 209 patients who had a recurrence. Among these 169 patients, the site of recurrence was intrahepatic only (*n* = 111, 65.7%), extrahepatic only (*n* = 19, 11.2%), or intra- and extra-hepatic (*n* = 39, 23.1%) (Table 2).

Several factors were associated with the site of recurrence (Fig. 1 and Table 2). Specifically, patients who had an R1 resection were more likely to experience an intrahepatic only recurrence (*n* = 36, 50.8%) compared with patients who had an R0 resection (*n* = 66, 32.9%) (*P* = 0.001). In contrast, while patients with well- (*n* = 39, 31.9%), moderately- (*n* = 26, 45.6%), or poorly differentiated (*n* = 18, 40.0%) tumors had a similar incidence of intrahepatic recurrence, the incidence of extrahepatic only and combined intra- and extra-hepatic recurrence were markedly higher among patients with a poorly differentiated tumor (extrahepatic only: well, *n* = 4, 3.3% vs moderate, *n* = 1, 1.8%; vs poorly, *n* = 3, 6.7%; combined intra- and extra-hepatic recurrence: well, *n* = 14, 11.5% vs moderate, *n* = 8, 14.0% vs poorly, *n* = 13, 28.9%) (both *P* < 0.05). Extrahepatic recurrence was also much more common among patients with pancreatic (*n* = 11, 9.2%) and other non-GI NET (*n* = 2, 9.1%) compared with gastrointestinal NET (*n* = 6, 4.4%) (*P* = 0.005). Perhaps not surprisingly, patients who presented with extrahepatic disease at initial diagnosis were more likely to recur with either extrahepatic disease only or combined intra- and extra-hepatic disease (combined intra- and extra-hepatic recurrence: extrahepatic disease at initial diagnosis, *n* = 8, 33.3% vs no-extrahepatic disease at initial diagnosis, *n* = 31, 12.0%; extrahepatic only: extrahepatic disease at initial diagnosis, *n* = 7, 29.2% vs no-extrahepatic disease at initial diagnosis, *n* = 12, 4.7%) (*P* < 0.001).

Of note, site of recurrence was associated with time of recurrence. Specifically, most early recurrences within the first 3 years after surgery were either intrahepatic only (*n* = 88, 79.3%) or combined intra- and extra-hepatic recurrences (*n* = 31, 79.5%), while late recurrences after 3 years were more often extrahepatic only (*n* = 9,

TABLE 2 Site of recurrence (n = 282)

Variable	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*P*-value
Type of Recurrence	No recurrence	Intrahepatic	Intra + extrahepatic	Extrahepatic	
	N = 113	*n* = 111	*n* = 39	*n* = 19	
Age, years, median (IQR)	59.3 (48.3-68.2)	58 (49.0-66.0)	58.0 (45.5-69.5)	56.0 (50.0-63.4)	0.89
Gender					0.24
Male	53 (36.6%)	59 (40.7%)	25 (17.2%)	8 (5.5%)	
Female	60 (43.8%)	52 (37.9%)	14 (10.2%)	11 (8.1%)	
Location of primary NET					0.005
Gastrointestinal	48 (34.8%)	67 (47.8%)	18 (13.0%)	6 (4.4%)	
Pancreas	49 (40.8%)	45 (36.7%)	16 (13.3%)	11 (9.2%)	
Other	16 (72.7%)	1 (4.6%)	3 (13.6%)	2 (9.1%)	
Functional status					<0.001
Non-functional	26 (19.4%)	79 (58.9%)	21 (15.7%)	8 (5.9%)	
Functional	47 (54.7%)	23 (26.7%)	9 (10.5%)	7 (8.1%)	
Grade of differentiation					
Well	65 (53.3%)	39 (31.9%)	14 (11.5%)	4 (3.3%)	
Moderate	22 (38.6%)	26 (45.6%)	8 (14.0%)	1 (1.8%)	
Poor	11 (24.4%)	18 (40.0%)	13 (28.9%)	3 (6.7%)	0.009
Lymph node status					<0.001
N0	83 (65.4%)	28 (22.1%)	13 (9.5%)	4 (3.2%)	
N1	25 (19.1%)	74 (56.5%)	23 (17.6%)	9 (6.9%)	
Synchronous disease					0.015
No	60 (47.2%)	43 (33.9%)	12 (9.5%)	12 (9.5%)	
Yes	53 (34.2%)	68 (43.9%)	27 (17.4%)	7 (4.5%)	
Treatment before liver surgery					<0.001
None	70 (37.0%)	79 (41.8%)	29 (15.3%)	11 (5.8%)	
Octreotide	32 (71.1%)	9 (20.0%)	3 (6.7%)	1 (2.2%)	
Chemotherapy	6 (23.1%)	11 (46.2%)	3 (11.5%)	5 (19.2%)	
Liver involvement					<0.001
≥50%	62 (31.9%)	88 (45.4%)	28 (14.4%)	16 (8.3%)	
<50%	48 (73.8%)	10 (15.4%)	7 (10.8%)	0	
Location					0.14
Unilobar	25 (26.0%)	52 (54.2%)	13 (13.5%)	6 (6.3%)	
Bilobar	50 (34.7%)	56 (38.9%)	25 (17.4%)	13 (9.0%)	
Intraoperative tumor ablation					0.011
No	101 (45.3%)	77 (34.8%)	30 (13.6%)	14 (6.3%)	
Yes	13 (22.0%)	32 (54.2%)	9 (15.3%)	5 (8.5%)	
Extrahepatic disease at diagnosis					<0.001
No	111 (43.0%)	104 (40.3%)	31 (12.0%)	12 (4.7%)	
Yes	2 (8.3%)	7 (29.2%)	8 (33.3%)	7 (29.2%)	
Margin status					0.001
R0	97 (49.2%)	66 (32.9%)	24 (12.0%)	12 (5.8%)	
R1	17 (22.4%)	36 (50.8%)	12 (16.4%)	8 (10.5%)	
Adjuvant therapy					
None	54 (43.2%)	43 (34.4%)	21 (16.8%)	7 (5.6%)	
Octreotide	13 (21.7%)	34 (56.7%)	8 (13.3%)	5 (8.3%)	
Chemotherapy	3 (9.4%)	19 (59.4%)	6 (18.8%)	4 (12.5%)	
Overall survival, 10-year (95%CI)	–	42.5% (24.9-59.0)	21.5% (5.3-44.9)	0%	<0.001

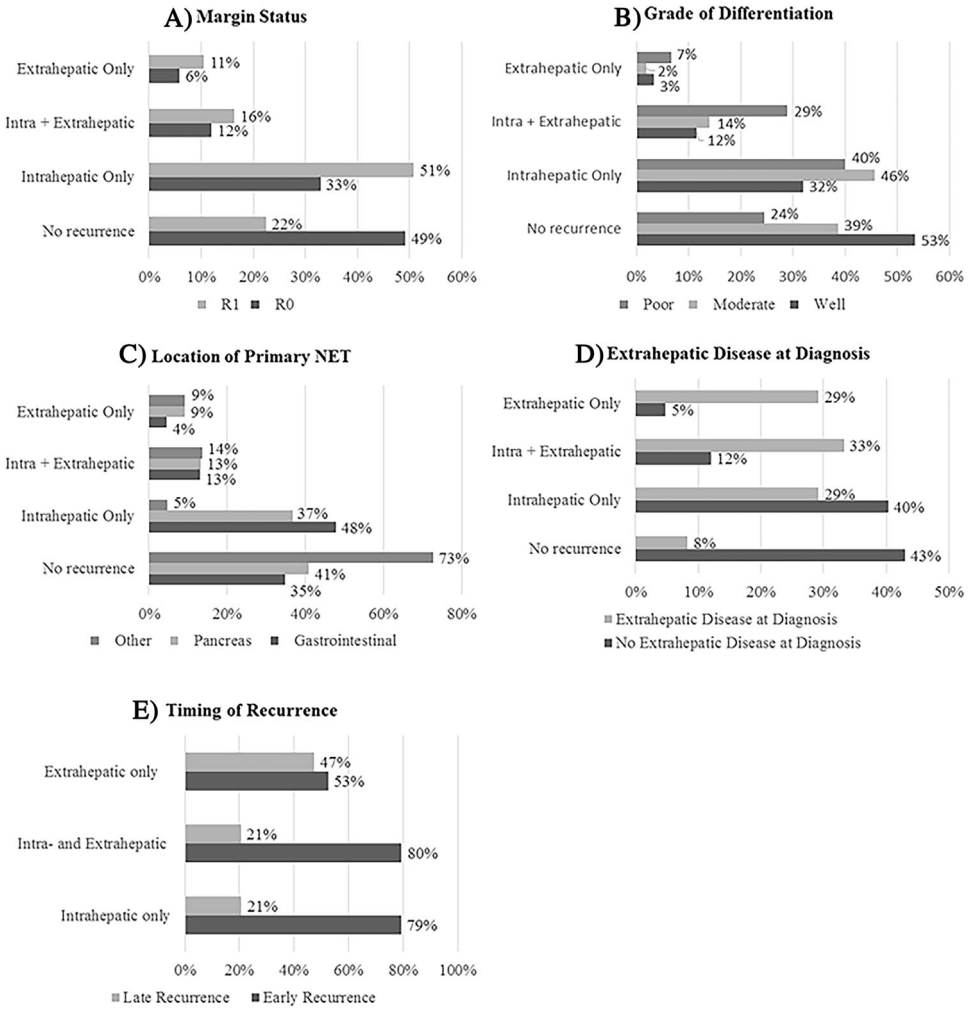

FIGURE 1 Histograms representing the incidence of (A) margin status, (B) grade of tumor differentiation, (C) location of primary NET, (D) extrahepatic disease at diagnosis, and (E) timing of recurrence among the different types of recurrence

47.4%) ($P = 0.03$). Timing of recurrence was also associated with prognosis, as patients who experienced an early recurrence had a worse prognosis (10-year OS: early recurrence, 41.8%, 95%CI, 29.2-53.8 vs late recurrence, 65.2%, 95%CI, 47.3-78.3) ($P = 0.001$). Compared with intrahepatic only recurrence, extrahepatic only and combined intra- and extra-hepatic recurrence were associated with a worse long-term outcome (10-year OS: intrahepatic only, 42.5%, 95% CI, 24.9-59.0 vs extrahepatic only, 0% and combined intra- and extra-hepatic, 21.5%, 95%CI, 5.3-44.0) (Fig. 2; $P < 0.001$).

3.4 | Treatment of recurrence and long-term outcomes

Among the 137 patients who had information available on the treatment of recurrence, most patients were treated with repeat surgery ($n = 49$, 36.6%), while 34 (23.5%) patients received a somatostatin analogue, 27 (18.6%) systemic cytotoxic chemotherapy, and 27 (21.4%) patients had IAT. Patients with intrahepatic only recurrence were treated more often with repeat surgery ($n = 39$, 43.8%), while patients with intra- and extra-hepatic recurrence were more frequently treated with somatostatin analogues ($n = 14$, 43.8%) and chemotherapy ($n = 12$, 37.5%; $P < 0.001$). Of note, late recurrence was treated more often with repeat surgical resection ($n = 9$, 40.9%) or with somatostatin analogues ($n = 9$, 40.9%) than with systemic chemotherapy ($n = 3$, 16.6%) and IAT ($n = 1$, 4.6%). In comparison, systemic chemotherapy ($n = 24$, 23.1%) and IAT ($n = 24$, 23.1%) were employed with similar frequencies as somatostatin analogues ($n = 25$,

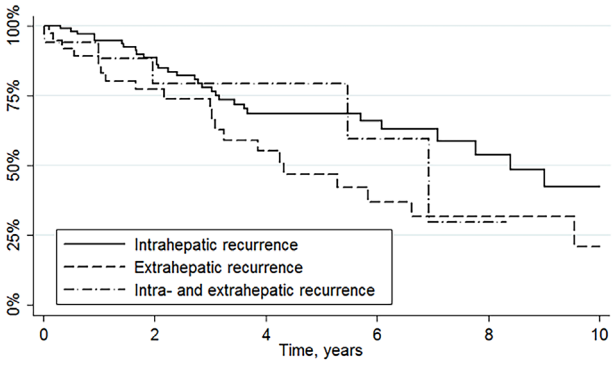

FIGURE 2 Kaplan-Maier overall survival curves stratified by site of recurrence

24.0%) and repeat surgical resection (*n* = 31, 29.8%) for the treatment of early recurrence (Table 3; *P* = 0.08).

Following treatment of recurrent disease, 10-year OS among patients who underwent repeat surgery and intra-arterial treatments was 60.3% (95%CI, 34.1-78.8) and 52.0% (95%CI, 30.6-69.9), respectively. In contrast, patients who received somatostatin analogue (45.9% 95%CI, 22.3-66.9) or systemic chemotherapy (0%) had a shorter long-term survival (Fig. 3; *P* = 0.001).

4 | DISCUSSION

While NET are derived from a wide variety of primary tumor sites, secondary metastatic disease is a common feature regardless of where the tumor originated. The presence of NELM is one of the most important predictors of survival, while also frequently impacting the quality of life of patients with NET.[6] Despite several nonsurgical therapies, surgery often is the cornerstone of the treatment of patients with NELM. In fact, several studies have evaluated and compared different treatment approaches for patients with NELM.[24–27] Most previous studies did not, however, focus on the treatment of recurrent NELM. The current study is important because, using a large, international, multi-institutional cohort of patients, we characterized the overall pattern of NELM recurrence following curative intent surgery and defined the incidence of recurrence to be 64.9% within a median follow up of 4.5 years. The majority of patients (72.7%) developed recurrence within 3 years after surgery. Several clinicopathological factors, such as functional status, presence of metastatic lymph nodes, grade of tumor differentiation, and liver involvement were associated with a higher likelihood of recurrence. Indeed, these clinicopathological characteristics were particularly associated with the risk of early versus late recurrence (Table 1). In turn, early recurrence was associated with a worse prognosis compared with late recurrence (10-year OS: early recurrence, 41.8%, 95%CI, 29.2-53.8 vs late recurrence, 65.2%, 95%CI, 47.3-78.3) (*P* = 0.001). These findings suggest that specific clinicopathological characteristics are more likely to impact long-term outcome by being associated with early recurrence.

The most common pattern of recurrence was intrahepatic (65.7%), while fewer patients had an extrahepatic component of recurrent disease (extrahepatic only, 11.2%; combined intra- and extrahepatic, 23.1%;). Patients with intrahepatic recurrence were more likely to have undergone an R1 resection and more often had poorly differentiated tumors. Patients with liver involvement ≥50% at the time of surgery were also more likely to have intrahepatic recurrence, while patients with <50% of liver involvement had a lower risk of any recurrence. Of note, patients with NELM from a pancreatic NET primary recurred more frequently at extrahepatic sites than in the liver (Table 2). Perhaps not surprisingly, pattern of recurrence seemed to impact long-term outcomes (Fig. 2). Specifically, patients who had an extrahepatic component of recurrent disease had a worse prognosis compared with patients who had only intrahepatic recurrence (10-year OS: intrahepatic only, 42.5%; extrahepatic only, 0%; combined intra- and extra-hepatic, 21.5%) (*P* < 0.001).

While repeat hepatectomy has been advocated as the treatment of choice for recurrent hepatocellular carcinoma[22] and colorectal liver metastasis,[20] data on different management options for patients with recurrent NELM are lacking. In the present study, surgery was the most common treatment choice of recurrent NELM (36.6%), while one fifth of patients received IAT (21.4%), one fourth were treated with somatostatin analogues (23.5%), and the remaining patients were received chemotherapy (18.6%). Surgery was the treatment of choice of patients with intrahepatic recurrence (43.8%), while patients with intra- and extra-hepatic recurrence more frequently received somatostatin analogues (43.8%) and those patients with extra-hepatic recurrence (75%) were more likely to receive chemotherapy. Patients who had early recurrence were equally treated with any type of surgical and non-surgical approach, while patients with late recurrence more frequently underwent surgery or somatostatin analogs. Repeat liver surgery has been demonstrated to be increasingly safe and effective for a wide variety of tumors.[28] In particular, the combination of surgical resection with ablation may provide a chance for tumor eradication among patients with a large tumor burden or with recurrent NELM.[29,30] In one study by Mayo et al that reported on 339 patients who underwent surgical management for NELM, the extent of

TABLE 3 Treatment of recurrence (*n* = 137)

Variable	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*P*-value
Treatment of recurrence	Somatostatin analogous	Chemotherapy	IAT	Surgery	
	N = 34	*n* = 27	*n* = 27	*n* = 49	
Site of recurrence					<0.001
Intrahepatic only	19 (21.4%)	12 (13.5%)	19 (21.4%)	39 (43.8%)	
Intra- and Extrahepatic	14 (43.8%)	12 (37.5%)	5 (15.6%)	1 (3.1%)	
Extrahepatic only	1 (25.0%)	3 (75.0%)	—	—	
Time of recurrence					0.077
Early	25 (24.0%)	24 (23.1%)	24 (23.1%)	31 (29.8%)	
Late	9 (40.9%)	3 (16.6%)	1 (4.6%)	9 (40.9%)	
Overall survival after treatment of recurrence, 10-year (95%CI)	45.9% (22.3-66.9)	0%	52.0% (30.6-69.9)	60.3% (34.1-78.8)	0.001

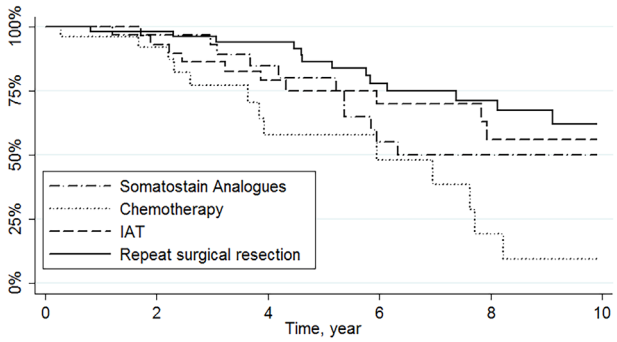

FIGURE 3 Kaplan-Maier overall survival curves stratified by the approach employed to treat the recurrence

hepatic resection among patients who underwent a repeat operation progressively diminished while ablation was used with increased frequency.[17] Collectively, data from previous reports as well as the current study, suggest that surgery, including with resection alone or with resection plus ablation should be considered for patients with recurrent disease—especially those with limited disease. For patients with more extensive disease, IAT may be a good option as this therapeutic approach was associated with a good long-term 10-year OS of over 50%.

This study has several limitations that should be considered when interpreting the results. First, the retrospective design of the study likely resulted in some confounding and selection/detection biases. In addition, because data were collected from multiple international centers, there was possible heterogeneity with the selection criteria and treatment approach for recurrent NELM disease. The inclusion of data from multiple centers does, however, increase the generalization of the findings. Finally, despite a large overall sample size, the relatively low number of patients with information on recurrence limited some of the subset analyses.

In conclusion, recurrence after curative intent surgery for NELM was common, occurring in three fourth of patients. Intrahepatic recurrence was the most common pattern of recurrence, although extrahepatic recurrence was also frequent. Pattern of recurrence was associated with specific clinical factors and impacted overall survival. When patients recur with NELM following initial surgical resection, therapy needs to be tailored with repeat liver resection considered when feasible as it may offer a reasonable long-term survival.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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